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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,584	05/03/2002	Audrey Goddard	10466/351	2701

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EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,584	GODDARD ET AL.	
	Examiner	Art Unit	
	Jon M. Lockard	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Jon Lockard.

2. Upon further consideration, and in order to make several new references of record in support of the standing utility and enablement rejections, the finality of the previous office action is withdrawn. It is noted that a Notice of Appeal and Appeal Brief have been filed. Applicant can request a refund for the associated fee or leave it as credit for future appeals. The delay and inconvenience to Applicant is regretted.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st Paragraph

4. Claims 1-5 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

5. The claims are directed to an isolated antibody that specifically binds to the polypeptide corresponding to SEQ ID NO:74, referred to in the specification as PRO1335. The specification does not disclose any secondary or tertiary structural features of the polypeptide to which this antibody binds, nor does it disclose any additional information regarding PRO1335 such as

subcellular location, timing of regulation during cellular differentiation, which hormones or transcription factors regulate PRO1335, and what physiological significance PRO1335 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility.

6. The record shows that Applicant relies primarily upon the asserted utility disclosed in Example 18, namely, that the claimed antibodies are useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of having a tumor (see, for example, pg 9 of the response received 05 November 2004; pp. 6-7 of the Appeal Brief received 01 August 2005). However, this asserted utility is not substantial for the following reasons.

7. In Example 18, the specification discloses that PRO1335 tested positive in a differential tissue expression analysis to detect underexpression/overexpression of PRO polypeptide-encoding nucleic acids in cancerous tumors (pp. 140-142). Quantitative PCR was used to detect differences in levels of cDNAs in cDNA libraries made from cancerous and normal tissues. Example 18 discloses that PRO1335 cDNA levels are: (1) higher in normal stomach as compared to stomach tumor; (2) higher in normal lung as compared to lung tumor; (3) higher in normal rectum as compared to rectum tumor; and (4) higher in normal skin as compared to melanoma tumor. There is no disclosure of how great a difference in cDNA levels was detected. While this disclosure may provide utility and enablement for PRO1335 DNA, it does not provide utility nor enablement for PRO1335 polypeptides or antibodies.

8. Applicants argue that if the gene is differentially expressed in cancer versus non-cancer tissue, then the encoded polypeptide and antibodies which bind it are useful in diagnostics. The Declarations of Grimaldi (second declaration) and Polakis discuss the likelihood that if the

nucleic acid is differentially expressed in tumors, then the encoded polypeptide will also be. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. Applicants also assert that the references of Alberts (Exhibits 2 and 3) and Lewin (Exhibit 4) support the statements of Grimaldi and Polakis.

9. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. While the Examiner agrees with the teachings of Alberts and Lewin that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts (Exhibit 2) also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (See Exhibit 2 at pg 453). Applicants also have submitted Exhibit 6 (Meric et al., 2002) which states the following:

> The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription.

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (See page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (See pages 973-974). While Exhibit 5 (Zhigang et al., 2004) provides an example of a high degree of correlation between protein and mRNA expression of a specific antigen, the art also teaches that, in organisms ranging from yeast to human, changes in mRNA levels are not predictive of changes in the encoded polypeptide levels, especially in cancerous cells. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (2003, Nature Biotechnology 21:976-977). Similarly, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung

adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. also disclose that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is disclosed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Lichtinghagen et al. (2002, European Urology. 42 :398-406) show a similar lack of correlation in matrix metalloproteinases (MMPs 2 and 9 and the tissue inhibitor of metalloproteinases 1 (TIMP-1) in human prostate cancer. After measuring differential expression at both the mRNA and protein level of the genes, they concluded that [C]omparison of mRNA and protein expression of MMP-2, MMp-9, and TIMP-1, respectively, did not show any significant relationships illustrating the necessity to study these components at both molecular levels" (See abstract, pg 398).

10. The art also shows that transcript levels do not necessarily correlate with protein levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA

transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 proteins in yeast. They concluded that "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

11. Applicants argue at pages 14-17 of the Appeal Brief (received 01 August 2005) that the Chen data (cited by Examiner in the Advisory Action and reiterated at ¶10 *supra*) supports Applicants' assertion that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression.

12. Applicant's arguments have been fully considered but are not found to be persuasive. While Chen et al. do teach a correspondence between mRNA expression and protein abundance

for some genes, this correlation was only observed in 17% (28/165) of the protein spots measured (See pg 311, left column, for example). Chen et al. clearly teach that mRNA levels do not predict protein levels, as they disclose at pg 304 that "[t]he use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of a protein present in a given cell or tissue" (See pg 304, right column).

13. As supported by the studies cited above, the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels, and the specification of the instant application has not disclosed that the PRO1335 polypeptide is either overexpressed or underexpressed to the extent that it could be use as a diagnostic marker for any cancer.

14. Given the asserted decrease in PRO1335 mRNA expression and the evidence provided by the current literature, one skilled in the art would not consider it, more likely than not, that a small decrease in expression (no quantitative data provided) would correlate with significantly decreased polypeptide levels. In the absence of information regarding whether or not PRO1335 protein levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1335 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research. Further research needs to be done to determine whether the small decrease in PRO1335 mRNA expression supports a role for the encoded polypeptide as a diagnostic marker in the cancerous tissue, such that the claimed antibodies which specifically

bind to the PRO1335 polypeptide could be used in diagnostics. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

15. Accordingly, the specification's assertion that the PRO1335 polypeptides and antibodies which bind them have utility in the fields of cancer diagnostics and cancer therapeutics is not substantial.

16. Applicants argue at pages 17-18 of the Appeal Brief (received 01 August 2005) that the arguments made by the PTO are not sufficient to satisfy the PTO's initial burden of offering evidence that one of ordinary skill in the art would reasonably doubt the asserted utility. Applicant states that the Examiner's initial burden is to establish that it is more likely than not that a person of ordinary skill would consider that any utility asserted by the applicant would be specific and substantial. Applicant indicates that all the relevant evidence of record must be considered by the Examiner.

17. Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner has made a *prima facie* showing that the claimed invention lacks utility and has

provided sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. Essentially, Applicant has not provided evidence to demonstrate that the PRO1335 polypeptide would more likely than not be overexpressed in normal stomach, lung, rectum, and skin tissue samples as compared to stomach, lung, rectum, and melanoma tumor samples, respectively. Accordingly, antibodies which bind the PRO1335 polypeptide of the instant application is not supported by a specific and substantial asserted utility or a well established utility. The Examiner has fully considered all evidence of record and has responded to each substantive element of Applicant's response. It is noted to Applicant that MPEP § 2107.02 (part VI) also states that "where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained".

18. Applicants argue at pages 28-29 of the Appeal Brief (received 01 August 2005) that the cases of *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q 881 (C.C.P.A. 1980), *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985), and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) are very similar to the present case. Aplicants argue the reasoning of the courts in all three cases that "[I]t is inherently faster and easier to combat illneses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities" applies to the asserted utility for the claimed antibodies of the Instant Application. Applicants further argue the opinion set forth in *Fujikawa*, 93 F.3d at 1564, *quoting Nelson*, 626 F.2d at 856; *see also Cross*, 753 F.2d at 1051 ("Successful in vitro testing will marshal resources and direct the expenditure of effort to further

in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility.").

19. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. The fact patterns of the cases cited by Applicant and of the Instant Application are significantly different, and the court decisions are not binding with regard to the instant rejection. For example, in all three cases the issue was whether or not there was a reasonable correlation between the disclosed *in vitro* results and *in vivo* activity. However, in the Instant Application, the Instant Specification as originally filed has not provided *any* evidence demonstrating the polypeptide to which the claimed antibody binds has any biological activity or is more abundant in normal stomach, lung, rectum, and skin tissue samples as compared to stomach, lung, rectum, and melanoma tumor samples, respectively, either *in vitro* or *in vivo*. Therefore, the issue of whether or not there exists a reasonable correlation between *in vitro* results/activity and *in vivo* results/activity in the Instant Application is irrelevant.

35 U.S.C. § 112, 1st Paragraph (Enablement)

20. Claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Summary

21. No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback**, can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JML
October 12, 2005

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